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An evaluation of the impact of *MAPT*, *SNCA* and *APOE* on the burden of Alzheimer and Lewy body pathology

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Abstract

The study investigates the effects of genetic factors on the pathology of Alzheimer's disease (AD) and Lewy body (LB) diseases, including Parkinson's disease and dementia with Lewy bodies. A multicenter autopsy series (762 brain samples) with AD, LB or vascular pathology was examined. We assessed the effects of the tau gene (*MAPT*) H1 haplotype, the H1-specific SNP rs242557, *APOE* and the α-synuclein gene (*SNCA*) 3′UTR SNP rs356165 on the burden of AD and LB pathology. We counted neurofibrillary tangles (NFTs) in four brain regions, senile plaques (SPs) in five and LBs in four. We also documented Braak NFT stage, brain weight and presence of vascular pathology. *MAPT* H1 associated with lower counts of NFTs in the middle frontal

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COMPETING INTERESTS
The Corresponding author (DWD) had had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CONTRIBUTORSHIP STATEMENT
CW designed the study, analyzed the data, drafted the manuscript and approved its final version.
OAR designed the study, analyzed the data, critically reviewed the manuscript and approved its final version.
KN performed genetic analysis, critically reviewed the manuscript and approved its final version.
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MJF analyzed genetic data, critically reviewed the manuscript and approved its final version.
DWD designed the study, performed pathology analysis, drafted the manuscript and approved its final version.

(P<0.001) and inferior parietal (P=0.005) cortices, and also with lower counts of SPs in the motor cortex (P=0.001). Associations of *MAPT* H1 with increased LB counts in the middle frontal cortex (P=0.011) and inferior parietal cortex (P=0.033) were observed but were not significant after multiple testing adjustment. The *APOE* ε4 allele was strongly associated with overall Alzheimer type pathology (all P≤0.001). *SNCA* rs356165 and the *MAPT* H1-specific SNP rs242557 did not associate with AD or LB pathology. This study shows for the first time that *MAPT* H1 is associated with reduced Alzheimer type pathology, which could have important implications for the understanding of disease mechanisms and their genetic determinants.

Keywords

MAPT; *SNCA*; *APOE*; Alzheimer pathology; Lewy body

INTRODUCTION

Alzheimer's disease (AD) and Parkinson's disease (PD) are common age-related neurodegenerative conditions that lead to significant cognitive and motor impairment. Pathologically, they are characterised by the accumulation of hyperphosphorylated tau or α-synuclein.[1] Disorders with tau deposition include AD and the tauopathies progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease, argyrophilic grain disease and tau-positive frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17T), whereas α-synuclein pathology is a core feature of PD, dementia with Lewy bodies (DLB), multiple system atrophy and pure autonomic failure.[2]

In humans six tau isoforms are generated by alternative splicing of exons 2, 3 and 10. Based on the number of conserved ~30 amino acid repeats in the microtubule binding domain, the six tau isoforms can be divided into those with 3 repeats (3R-tau) and 4 repeats (4R-tau). In AD, tau deposition in neurofibrillary tangles (NFTs) consists of approximately equal amounts of 3R-tau and 4R-tau, whereas the "pure" tauopathies CBD and PSP display mostly 4R-tau deposits.[3] In addition to the accumulation of tau in NFTs, neuropil threads and dystrophic neurites, AD brains display numerous senile plaques (SPs) of which aggregated beta-amyloid (Aβ) is a key component. In contrast, the pathological hallmark of the synucleinopathies PD and DLB is the presence of α-synuclein-positive Lewy bodies (LBs) and Lewy neurites. In PD, LBs are found prominent in vulnerable brainstem nuclei, whereas they extend to neocortical areas in DLB and PD dementia.[4]

While early views favoured AD, tauopathies and synucleinopathies as mutually exclusive clinicopathologic entities, a growing body of evidence indicates an overlap exists at the clinical, genetic, pathologic and biochemical levels.[2] Clinically, the incidence of extrapyramidal symptoms such as bradykinesia, rigidity and gait impairment in AD patients is higher than expected in age-matched populations.[5] Conversely, dementia is a core feature of DLB and it is present in up to 80% of patients with PD 17 years after disease onset.[6] Pathologically, LBs can be identified in 30% to 60% of AD patients, with predominance in the amygdala;[7] one study found that rates tend to be higher among those AD patients with a high load of neuritic plaques.[8] In addition, most cases of LB disease (LBD) are accompanied by varying degrees of concurrent Alzheimer type pathology, and the finding of an association between cortical LBs and neuritic stage has led to the hypothesis that Aβ triggers both AD and LB pathology.[9] Neuronal co-localization of α-synuclein and tau has been documented in patients with LBD, AD and AD with LBs,[10] and phosphorylated forms of α-synuclein and tau were identified in synaptic-enriched fractions of frontal cortex from LBD and AD patients.[11] Additional evidence from various models, including MPTP-induced neurodegeneration in rodents, α-synuclein transgenic

mice and *in vitro* studies, point to a molecular interplay between Aβ, tau and α-synuclein. [12, 13]

In families with dominantly inherited PD due to mutations in the α-synuclein gene (*SNCA*) or the *leucine-rich repeat kinase 2* gene (*LRRK2*), pleomorphic pathology has been reported including LBs and tau-positive inclusions.[14, 15] Moreover, the most consistent genetic risk factor implicated in AD (the *APOE* ε4 allele) has been associated with the co-occurrence of Alzheimer type pathology in non-AD tauopathies and in synucleinopathies, as well as with the presence of LBs in AD.[16, 17] Mutations and copy-number abnormalities in *SNCA* cause PD and DLB, while genetic variation at the *SNCA* locus (including the *SNCA* 3′UTR SNP rs356165) has been associated with risk of PD and, more recently, with the burden of Alzheimer type pathology (Braak NFT stage).[18, 19] Furthermore, mutations in the tau gene (*MAPT*) cause FTDP-17T, and the H1 haplotype at the *MAPT* locus has been associated with several tauopathies including PSP and CBD;[20] yet *MAPT* H1 has also been implicated in risk of PD and PD dementia.[21, 22]

In the present study we examined the effects of the *MAPT* H1 haplotype, the H1-specific SNP rs242557, *APOE*, and the *SNCA* 3′UTR SNP rs356165 on the burden of AD and LB pathology in an autopsy series of 762 cases.

DESIGN/METHODS

Case selection

The 762 brains in this sample of convenience were from the Mayo Clinic Jacksonville brain bank for neurodegenerative disorders and were obtained from 1993 to 2004. Some had been part of the State of Florida Alzheimer Disease Initiative (n=414), the Einstein Aging Study (P01AG03949-25; n=57), the Mayo Clinic Jacksonville Memory Disorders Clinic (n=103), the University of Miami/National Parkinson Foundation Brain Endowment Bank (n=25), the Udall Center for Parkinson's Disease Research (P50NS40256; n=25), hospital autopsies or referrals from private pathologists or institutions (n=114) or the Society for Progressive Supranuclear Palsy Brain Bank program (n=24). Clinical diagnoses were dementia disorders in 631 cases (82% considered to be Alzheimer type dementia), while 70 had clinical diagnoses of movement disorders (71% considered to have PD) and 61 were cognitively normal or had mild cognitive impairment, history of stroke or a psychiatric disorder (depression being most common). Except for the Einstein Aging Study, subjects were not part of a prospective, standardised or longitudinal clinical study. A family history of neurologic disease was noted in 99 cases (13%), although this was also not systematically assessed. The study was approved by the Mayo Clinic Institutional Review Board and informed consent for brain donation was obtained from legal next-of-kin.

The median age at death was 81 years (25^{th} – 75^{th} percentiles: 74 – 86 years), there were 369 men (48%) and 393 women (52%), and all 762 individuals (100%) were of Caucasian descent. Total brain weight was calculated based on weight of the fixed hemi-brain.

All brains underwent complete neuropathologic macroscopic and microscopic evaluations, the latter with hematoxylin-eosin (H&E) and immunohistochemical stains and thioflavin-S fluorescent microscopy. Cases were selected based on the presence of Alzheimer, Lewy body or vascular pathology and included cases with combined pathology and cases with no significant pathology or mild pathologic abnormalities of the Alzheimer type (pathologic aging = many SPs and sparse or no NFTs, senile changes = sparse SPs and sparse or no NFTs) or Lewy body pathology not conforming to common classifications of Lewy body disease (e.g., amygdala-predominant Lewy bodies [7]). As the method used for quantification of Alzheimer type pathology, thioflavin-S, like thiazin red fluorescent

microscopy, does not reliably detect 4R-tau inclusions, cases with PSP and CBD were not included. Also excluded were cases with multiple system atrophy, frontotemporal lobar degeneration and any other major non-Alzheimer degenerative disease process.

Histology and immunohistochemistry

All brains were evaluated for Alzheimer type pathology using thioflavin-S fluorescent microscopy.[7] SPs were counted in five brain regions (maximal density of SPs per field at x100 magnification in medial frontal gyrus – MF, superior temporal gyrus – ST, inferior parietal gyrus – IP, motor cortex – MTR, and visual cortex – VC). There was a ceiling effect since SP counts were truncated at more than twice the number needed to meet Khachaturian criteria for AD,[23] therefore SP counts range from 0 to 50 (all cases with ≥50 SPs per field were scored as 50). The method used (thioflavin-S) did not allow to discriminate between diffuse plaques and neuritic plaques. NFTs were counted in four brain regions (maximal density of NFTs per field at x400 magnification in MF, ST, IP, and hippocampal CA1 – CA1); the Braak NFT stage [24] was also determined based upon distribution of NFTs.

All samples with Alzheimer type pathology underwent screening for LB pathology using α-synuclein immunohistochemistry (see below). Evaluation of LB pathology in Alzheimer type pathology-negative individuals was performed in two stages. First, examination of brainstem nuclei (substantia nigra, locus ceruleus, and dorsal motor nucleus of vagus nerve) with H&E staining assessed the presence of neuronal loss or LBs. Those cases with evidence of neuronal loss or LB pathology underwent α-synuclein immunostaining using a polyclonal rabbit antibody (NACP, Mayo Clinic, Jacksonville, FL). In all other cases with no neuronal loss in vulnerable brainstem nuclei, a section of amygdala was screened for LBs.[7] If detected in the amygdala, then these cases were also studied for cortical and brainstem LBs. Presence and distribution of LBs were scored from 0 to 4 (0, no LBs; 1, amygdala predominant; 2, brainstem predominant – BLBD; 3, brainstem and limbic = transitional LBD – TLBD; 4, brainstem and diffuse cortical – DLBD). Cortical LBs were counted in four brain regions (maximal density of cortical LBs per field at x200 magnification in MF, ST, IP, and cingulate gyrus – CG).

Cerebrovascular pathology was assessed on all cases using a semiquantitative scale similar to that previously reported.[25] Briefly, cases with no cerebrovascular lesions were scored 0, those with minimal cerebrovascular pathology (including 1 to 2 small lacunes, mild CAA, or mild leukoencephalopathy) were scored 1, those with moderate lesions (including more than 2 lacunes, severe CAA, or diffuse leukoencephalopathy) were scored as 2, and those with marked cerebrovascular pathology (including old cortical infarcts, multiple microinfarcts, or hippocampal sclerosis) were scored 3. For purposes of analysis, cases with scores of 2 and 3 were grouped as having vascular pathology and those with scores of 0 and 1 were considered to lack vascular pathology.

Genotyping

In all 762 subjects, DNA was obtained from frozen brain tissue using standard protocols. Each sample was genotyped for *MAPT* H1/H2 (SNP rs1052553 A/G, A=H1, G=H2), *APOE*, and the *SNCA* 3′UTR SNP rs356165 (G/A). Additionally, a subset of 690 samples was genotyped for the H1-specific (i.e. only polymorphic on H1 chromosomes) SNP rs242557 (A/G), given a previously reported association with risk for AD.[26] All genotypes except *APOE* were determined using a Sequenom MassArray iPLEX platform (Sequenom, San Diego, CA) and analysed with Typer 4.0 software (also from Sequenom). The *APOE* genotype was determined using TaqMan chemistry. All primer sequences are available upon request. Genotype failure occurred in less than 2% of samples.

Statistical analysis

We examined the association of *MAPT* H1/H2, *MAPT* rs242557, *APOE* and *SNCA* rs356165 genotypes with a variety of different endpoints (LB count, LBD score, NFT count, Braak NFT stage, SP count, vascular disease, and brain weight), and the statistical tests used to evaluate these associations were determined by the nature of the given endpoint (count, censored, binary categorical or numerical). For LB and NFT counts, associations with genotypes were evaluated using negative binomial regression models. With a ceiling of 50 counts, SP counts were censored at a value of 49 counts, and as such parametric survival regression models were used to examine associations between SP count and genotypes. For LBD score (<2 vs. ≥2), Braak NFT stage (<5 vs. ≥5) and vascular disease, logistic regression models were used to evaluate associations with genotypes; for easier interpretation, LBD score was dichotomized as <2 vs. ≥2 as LBD stage ≥2 indicates disease outside the brainstem, and Braak NFT stage was dichotomized as <5 vs. ≥5 due to the fact that Braak NFT stage ≥5 is considered concrete evidence of AD. Associations between brain weight and genotypes were examined using linear regression models.

Single variable models (i.e. models with no adjustment) were considered in all regression analyses in an exploratory analysis, as well as multivariable models adjusting for the known potentially confounding variables age, sex and *APOE* (only in models involving NFT count, SP count, Braak NFT stage, and brain weight) in the primary analysis. Interactions between genotypes were also considered. Due to the high concentration of LB counts equal to zero and SP counts at the ceiling of 50, these variables were converted into binary categorical variables (>0 and <50, respectively) for ease of presentation, though the actual counts were used in performing statistical tests.

We adjusted for the number of statistical tests that were performed as follows. We defined a family of statistical tests as all tests evaluating the associations of outcomes with a given SNP, resulting in a different family of tests in evaluating associations of endpoints with *MAPT* H1/H2 genotype, with *MAPT* rs242557 genotype, with *APOE* genotype, and with *SNCA* rs356165 genotype. For each family of statistical tests, multiple testing was adjusted for using single-step minP procedure with 10,000 permutations of genotype labels to determine the level of significance that controls the family-wise error rate at 5%; P-values less than or equal to this level were considered statistically significant.[27] All statistical analyses were performed using S-Plus (version 8.0.1; Insightful Corporation, Seattle, Washington).

RESULTS

Overall pathologic findings are summarized in Table 1. There was evidence of an association between the *MAPT* H1 haplotype (rs1052553 A-allele) and Alzheimer type pathology (Table 2), with and without adjustment for age, sex and *APOE* genotype.

The H1 allele was associated with lower NFT counts in three (MF, ST, and IP) of the four regions examined (all P≤0.027), and also with a lower Braak NFT stage (P=0.037). Similarly, SP counts were lower among *MAPT* H1 carriers compared to non-carriers in three (MF, ST, and MTR) of the five regions examined (all P≤0.048). After correction for multiple testing (P≤0.0054 considered statistically significant), H1 remained associated with lower NFT counts in two regions (MF, P<0.001; IP, P=0.005) and with lower SP counts in one region (MTR, P=0.001). Stratification based on the *APOE* genotype did not influence the effect of *MAPT* H1 on pathologic measures (P≥0.25 for all H1-ε4 interactions). *MAPT* H1 was also associated with increased LB count in two regions (MF, P=0.011; IP, P=0.033), and also with increased LB score (P=0.019), however none of these findings remained significant after multiple testing adjustment. Given the unexpected associations of *MAPT*

H1 with lower NFT and SP counts, we further examined these associations in a sensitivity analysis involving only those cases with Alzheimer's disease pathology (web-only Table 1). In this smaller sample with lower power to detect associations, results were generally similar, with *MAPT* H1 associated with lower NFT counts (MTR and IP regions) and with lower SP counts (MTR region). The H1-specific SNP rs242557 did not show evidence of an association with pathologic measures (all P≥0.063, web-only Table 2).

There was a strong association between the *APOE* ε4 allele and Alzheimer type pathology (Table 3).

The ε4 allele was associated with higher NFT and SP counts in all regions examined, as well as with a higher Braak NFT stage and lower brain weight (all P≤0.001), and all of these findings remained significant after correction for multiple testing (P≤0.0056 considered statistically significant). There was no evidence of an association between *APOE* ε4 and LB counts or LB score (all P≥0.19).

The *SNCA* 3′UTR SNP rs356165 did not show association with any of the PD/LBD pathological endpoints examined, including LB counts and LB score (all P≥0.16; data not shown). As expected, *SNCA* rs356165 did not associate with Alzheimer type pathology (all P≥0.41). Given previous evidence of an interaction between *SNCA* and *MAPT* H1 in determining risk of PD,[21] interaction between rs356165 and *MAPT* H1 was examined for LB pathology by stratifying the effect of *MAPT* H1 based on the rs356165 genotype. We observed no evidence of an interaction between rs356165 and *MAPT* H1 regarding LB counts (all P≥0.58) or LB score (P=0.51) (web-only Table 3).

DISCUSSION

Our study employed a large autopsy series to examine the role of *MAPT* (H1/H2 and the H1-specific SNP rs242557), *APOE* (ε4 allele) and *SNCA* (rs356165) in determining the density of LBs and Alzheimer type pathology. We identified a novel association between *MAPT* H1 and reduced severity of Alzheimer type pathology. Specifically, after correction for multiple testing, H1 was associated with lower NFT counts (MF, IP) and SP counts (MTR), and these effects were independent of *APOE* genotype, age, and sex. Furthermore, similar trends that did not reach significance after multiple testing correction were observed for NFT counts (ST), SP counts (MF and ST), and Braak NFT stage.

Our findings suggest a protective effect of the *MAPT* H1 haplotype on severity of Alzheimer type pathology, which has several major implications. Although initially surprising given strong and consistent evidence linking the *MAPT* H1 haplotype with an increased risk for the 4R-tauopathies PSP and CBD, recent genome-wide association studies have failed to identify any association of *MAPT* with risk of AD.[28, 29] Moreover, meta-analysis of reported genetic association studies in AD does not find a significant association with *MAPT*.[30] Data from studies in three autopsy-confirmed Caucasian AD patient-control series (combined sample: 655 patients and 380 controls) also do not support H1 increasing risk for developing AD.[26, 31]

Previous *in vitro* studies showed that H1 is more efficient at promoting *MAPT* expression compared to H2,[32] yet our data show this does not translate into pathologic AD lesions and may be associated with reduced burden of NFTs and SPs. Possible explanations include interactions (e.g. with *glycogen synthase kinase-3β – GSK3B*) that alter *MAPT* transcription or propensity of tau to form aggregates. In support of this hypothesis, the previously reported 2-SNP haplotype in *GSK3B* only associated with an increased risk of PD and AD among carriers of at least one *MAPT* H2 allele and not in H1/H1 homozygotes, suggesting a protective effect of H1.[33, 34] Interestingly, our data indicate that *MAPT* H1 is associated

with reduction of not only NFTs, but also SPs. This emphasizes the importance of tau in AD and is consistent with the known correlation between NFT pathology and presence and severity of dementia in AD,[35] indicating our findings may have clinical implications.

We identified associations of *MAPT* H1 with severity of LB pathology that were significant at P≤0.05; however, none of these withstood correction for multiple testing. Of note, power to detect such associations was limited due to the significant number of cases with zero LB counts, and the possibility of Type II error is important to consider. Despite the lack of significance after multiple testing correction, our findings appear to be consistent with previous findings from association studies that consistently reported H1 being a risk factor for clinically-defined PD,[22] which would be expected to be associated with brainstem and in most cases cortical LBs.[4, 36, 37] It should be noted that one study failed to identify an association between *MAPT* H1 and pathologically-confirmed PD.[38] This may stem from differences in clinical and pathological ascertainment of PD or indicate that these genetic factors determining risk are not always associated with end-point quantitative measures. Additionally, analysis of LB score included cases with amygdala predominant LBs, which may have obscured an association. Given the association of *MAPT* H1 with clinical PD and limitations of the present study, future studies with larger numbers of patients with LBD are needed to better characterize the effect of *MAPT* H1 on LB pathology.

Consistent with previous clinical and pathological studies, our results showed a strong association between the *APOE* ε4 allele and Alzheimer type pathology, with an increase in NFT counts, Braak NFT stage and SP counts, and a decrease in brain weight among ε4 carriers, all of which remained significant after multiple testing correction.[39] The stronger effect on SP than NFT is consistent with the association of *APOE* ε4 with amyloid, but not tau measures in imaging and CSF studies of prospectively studied humans over a wide age range.[40] In contrast to the protective effect of H1, the brain regions affected by *APOE* ε4 included those areas known to be vulnerable to Alzheimer type pathology (CA1 and IP).

In a recent study, Peuralinna and colleagues identified an association between *SNCA* intron 4 SNP rs2572324 and Braak NFT stage in an autopsy series (n=272).[19] Furthermore, there was a trend toward an association for four additional *SNCA* SNPs, including the 3′UTR SNP rs356165. In contrast, our results did not find any association between rs356165 and AD or LB pathology. These discrepant results are not related to sample size issues as our overall series and the number of cases with LB pathology were larger. Possible explanations include differences in study design (population-based in theirs vs. consecutive autopsy series in ours) and pathologic evaluation, or may reflect population specificity (relatively homogeneous Finnish population in theirs vs. admixed US population in ours).

Given that genetic variation at both the *MAPT* and *SNCA* loci was suggested to alter risk for PD and PD dementia by means of an interaction,[21] we investigated whether rs356165 influences the effect of H1 on LB pathology. We observed no evidence of an interaction between rs356165 and *MAPT* H1 for LB pathology in our series.

CONCLUSION

The results of our study indicate that the *MAPT* H1 haplotype is associated with reduced severity of Alzheimer type pathology and that this effect is independent from age, sex and *APOE*. This provides important novel mechanistic insights into the complex pathogenesis of AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Summary of pathologic findings

Variable	Summary (N=762)
LB count	
Middle frontal (>0)	221 (29%)
Counts in those with >0	2 (1, 1, 5, 26)
Superior temporal (>0)	262 (34%)
Counts in those with >0	6 (1, 3, 12, 51)
Inferior parietal (>0)	194 (25%)
Counts in those with >0	2 (1, 1, 4, 22)
Cingulate gyrus (>0)	256 (34%)
Counts in those with >0	7 (1, 3, 13, 45)
LBD score	
0 (no LBs)	437 (57%)
1 (amygdala predominant)	68 (9%)
2 (brainstem predominant)	6 (1%)
3 (limbic)	94 (12%)
4 (diffuse cortical)	157 (21%)
NFT count	
Middle frontal	2 (0, 0, 7, 46)
Superior temporal	5 (0, 1, 12, 47)
Inferior parietal	3 (0, 0, 10, 60)
Hippocampal CA1	8 (0, 2, 15, 55)
Braak NFT stage	
Overall	5 (0, 4, 6, 6)
0–II	96 (13%)
III–IV	157 (21%)
V–VI	507 (67%)
SP count	
Middle frontal (<50)	150 (20%)
Counts in those with < 50	7 (0, 0, 29, 48)
Superior temporal (<50)	202 (27%)
Counts in those with < 50	15 (0, 0, 32, 48)
Inferior parietal (<50)	148 (20%)
Counts in those with < 50	5 (0, 0, 26, 48)
Motor cortex	18 (0, 9, 30, 50)
Visual cortex	26 (0, 13, 45, 50)
Vascular disease	212 (28%)
Brain weight (g)	1080 (440, 960, 1200, 1630)

The sample median (minimum, 25th percentile, 75th percentile, maximum) is given for numerical variables. LB = Lewy body, NFT = neurofibrillary tangle, SP = senile plaque. Information was unavailable for the following variables: LB count (MF: N=2, ST: N=1, IP: N=3, CG: N=7), NFT count (ST: N=1, IP: N=3, CA1: N=6), Braak NFT stage (N=2), SP count (ST: N=2, IP: N=4, MTR: N=42, VC: N=13), and brain weight (N=25).

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Table 2

Associations between *MAPT* H1/H2 (rs1052553 A/G) and LB, AD and vascular pathology, and brain weight

	Genotype			P-values	
Outcome measure	**H2/H2 (N=46)**	**H1/H2 (N=245)**	**H1/H1 (N=469)**	**No adjustment**	**Adjusting for age and sex** *
LB count					
Middle frontal (>0)	6 (13%)	65 (27%)	149 (32%)	0.026	0.011
Superior temporal (>0)	7 (15%)	81 (33%)	173 (37%)	0.12	0.10
Inferior parietal (>0)	7 (15%)	56 (23%)	130 (28%)	0.059	0.033
Cingulate gyrus (>0)	8 (17%)	79 (33%)	168 (36%)	0.12	0.10
LBD score (≥ 2)	8 (17%)	80 (33%)	168 (36%)	0.028	0.019
NFT count					
Middle frontal	4 (0, 2, 14, 46)	3 (0, 0, 8, 30)	2 (0, 0, 5, 35)	<0.001	<0.001
Superior temporal	7 (0, 3, 13, 37)	6 (0, 1, 13, 36)	5 (0, 1, 11, 47)	0.045	0.027
Inferior parietal	7 (0, 2, 12, 60)	4 (0, 0, 10, 57)	3 (0, 0, 8, 40)	0.002	0.005
Hippocampal CA1	12 (0, 5, 16, 38)	7 (0, 2, 13, 55)	9 (0, 2, 16, 55)	0.22	0.36
Braak NFT stage (≥ 5)	41 (89%)	159 (65%)	307 (66%)	0.040	0.037
SP count					
Middle frontal (<50)	6 (13%)	41 (17%)	102 (22%)	0.078	0.048
Superior temporal (<50)	8 (17%)	56 (23%)	137 (29%)	0.034	0.016
Inferior parietal (<50)	5 (11%)	44 (18%)	97 (21%)	0.12	0.074
Motor cortex	23 (2, 14, 46, 50)	18 (0, 10, 32, 50)	18 (0, 9, 30, 50)	<0.001	0.001
Visual cortex	30 (0, 19, 50, 50)	28 (0, 14, 45, 50)	26 (0, 13, 45, 50)	0.018	0.23
Vascular disease	13 (28%)	78 (32%)	121 (26%)	0.18	0.086
Brain weight	1060 (780, 920, 1175, 1450)	1080 (700, 960, 1180, 1600)	1090 (440, 980, 1200, 1630)	0.16	0.063

The sample median (minimum, 25th percentile, 75th percentile, maximum) is given for numerical variables. P-values result from negative binomial regression models (LB counts and NFT counts), parametric regression survival models considering counts of 50 censored (SP counts), logistic regression models (LBD score ≥ 2, vascular disease, Braak stage ≥ 5), and linear regression models (brain weight), all under an additive model.

* For models involving NFT count, SP count, Braak stage, and brain weight, *APOE* genotype was adjusted for in addition to age and gender.

P-values ≤ 0.0054 are considered statistically significant after a single-step minP adjustment for multiple testing. Numbers account for genotype failure. LB = Lewy body, LBD = Lewy body disease, NFT = neurofibrillary tangle, SP = senile plaque.

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Table 3

Associations between *APOE* ε4 and LB, AD and vascular pathology, and brain weight

	APOE ε4 allele count			P-value	
Outcome measure	**0 "ε4" alleles (N=348)**	**1 "ε4" allele (N=331)**	**2 "ε4" alleles (N=78)**	**No adjustment**	**Adjusting for age and sex**
LB count					
Middle frontal (>0)	94 (27%)	105 (32%)	21 (27%)	0.84	0.85
Superior temporal (>0)	113 (33%)	124 (37%)	24 (31%)	0.47	0.40
Inferior parietal (>0)	86 (25%)	88 (27%)	20 (26%)	0.17	0.19
Cingulate gyrus (>0)	107 (31%)	123 (37%)	25 (32%)	0.87	0.75
LBD score (≥ 2)	110 (32%)	121 (37%)	25 (32%)	0.46	0.44
NFT count					
Middle frontal	1 (0, 0, 6, 40)	2 (0, 0, 6, 46)	6 (0, 2, 11, 27)	0.003	0.001
Superior temporal	3 (0, 0, 10, 47)	6 (0, 2, 12, 37)	10 (0, 4, 16, 35)	<0.001	<0.001
Inferior parietal	2 (0, 0, 8, 57)	4 (0, 1, 9, 60)	8 (0, 3, 13, 33)	0.001	<0.001
Hippocampal CA1	5 (0, 2, 12, 38)	10 (0, 3, 18, 55)	12 (0, 7, 18, 55)	<0.001	<0.001
Braak stage (≥ 5)	192 (55%)	241 (73%)	72 (92%)	<0.001	<0.001
SP count					
Middle frontal (<50)	99 (28%)	45 (14%)	4 (5%)	<0.001	<0.001
Superior temporal (<50)	135 (39%)	60 (18%)	5 (6%)	<0.001	<0.001
Inferior parietal (<50)	103 (30%)	41 (13%)	3 (4%)	<0.001	<0.001
Motor cortex	16 (0, 5, 27, 50)	20 (0, 11, 30, 50)	25 (0, 13, 43, 50)	<0.001	<0.001
Visual cortex	22 (0, 7, 35, 50)	32 (0, 18, 50, 50)	48 (1, 24, 50, 50)	<0.001	<0.001
Vascular disease	104 (30%)	90 (27%)	16 (21%)	0.11	0.17
Brain weight	1100 (684, 1000, 1240, 1630)	1080 (440, 960, 1160, 1540)	1050 (680, 928, 1195, 1540)	<0.001	0.002

The sample median (minimum, 25th percentile, 75th percentile, maximum) is given for numerical variables. P-values result from negative binomial regression models (LB counts and NFT counts), parametric regression survival models considering counts of 50 censored (SP counts), logistic regression models (LBD score ≥ 2, vascular disease, Braak stage ≥ 5), and linear regression models (brain weight), under an additive model.

P-values ≤ 0.0056 are considered statistically significant after a single-step minP adjustment for multiple testing. Numbers account for genotype failure. LB = Lewy body, LBD = Lewy body disease, NFT = neurofibrillary tangle, SP = senile plaque.